

~~Sub 1~~ type one interferon to said animal such that the type one interferon is ingested immediately upon [after] oral administration.

~~Sub 2~~ 8. (Amended) A method of decreasing the severity or frequency of a relapse of multiple sclerosis in a human comprising the step of orally administering a type one interferon to said animal such that the type one interferon is ingested immediately upon [after] oral administration.

~~Sub 3~~ 19. (Amended) A method of decreasing the levels of a cytokine in an individual having multiple sclerosis, comprising the step of orally administering a type one interferon to said individual, wherein said cytokine is selected from the group consisting of TGF- β , IL-2, IL-10, IFN- γ and ICAM-1; and wherein said type one interferon is ingested immediately upon oral administration.

REMARKS

Applicant thanks the Examiner for the thorough reading of the application. The following comments are directed toward the Office Action of July 16, 1997. Claims 1-20 are pending currently. Claims 1, 8 and 19 have been amended herein. No new matter has been added.

Outstanding issues:

- Claims 1-20 stand rejected under 35 U.S.C. § 102(a).
- Claims 1-20 stand rejected under 35 U.S.C. §103(a).

The 35 U.S.C. §102(a) and 35 U.S.C. §103(a) Rejections:

Claims 1-4, 6-11, and 13-20 stand rejected under 35 U.S.C. §102(a) as being anticipated by Cummins, U.S. Pat. No. 5,019,382. Additionally, claims 5 and 12 stand rejected under 35 U.S.C. §103 as being obvious in view of Cummins, and claims 1-20 stand rejected under 35 U.S.C. §103 as being obvious in light of Cummins and Shibutani. All rejections are respectfully traversed.

Applicant believes that the differences in Applicant's opinion regarding novelty and obviousness and the Examiner's opinion on these subjects involves semantics. Applicant submits that one with average skill in the art and virtually any clinician would interpret the phrase "oral administration" to mean a substance taken by mouth, swallowed, and ingested; i.e., retention of the substance in the mouth for any length of time is not a step required of "oral administration." Further, it is clear Applicant presumed this interpretation would be used. Note that Applicant recites "ingested" in several instances in the specification (see, e.g., p.6, lines 1, 5, and 14; p. 11, lines 6 and 16; p. 15, lines 11 and 17; p. 51, line 12; and p.

60, line 12); as well as "fed" (see, e.g., p.10, lines 12 and 19; page 19, line 4; p. 24, lines 9, 14, 16 and 23; p. 31, line 9; etc.), a word which presumes ingestion. Further, at page 50, lines 11-15, Applicant concludes:

The present invention demonstrated that murine species-specific (mIFN- α) and hrIFN- α delivered to *the stomach and small intestine* of mice suppressed clinical relapse in chronic relapsing experimental autoimmune encephalomyelitis (CR-EAE), decreased inflammation and suppressed the adoptive transfer of EAE.

(emphasis added). Applicant does not state expressly nor does Applicant imply that "oral administration", in general or specifically in association with the present invention, requires retaining the type one interferon substance in one's mouth, or that "oral administration" does not encompass immediate ingestion. Moreover, the claims as filed recited "ingested" and have been amended herein to clarify that ingestion takes place "immediately." Thus, Applicant presumes that the Examiner will bestow upon the phrase the meaning of "oral administration" as it is known in the art.

Conversely, the prior art cited by the Examiner *does* stipulate that administration be targeted to the oral and pharyngeal mucosa. The Cummins '382 patent teaches repeatedly that any type one interferon form should have maximum contact with the oral and pharyngeal mucosa (see, e.g., col. 3, line 8; col. 4, lines 13-18; col .5, lines 1-4; etc.), that is, be retained in the mouth. Indeed, Cummins' teaching is unequivocal: At col. 4, lines 37-43 the patent states "[i]t

is *critical* that the interferon be administered in a dosage form adapted to assure *maximum contact* of the oral and pharyngeal mucosa of the human or animal undergoing treatment....” (emphasis added).

Cummins was not alone in this view. In fact, at one point it was thought commonly that *any* form of oral administration was not feasible. For example, in a manuscript regarding the absence of biological effects of orally administered interferon- β , the authors comment that to assess biological effectiveness of interferon (IFN) administered orally, they measured serum IFN and several proteins and metabolites induced by type I IFN after oral administration of recombinant IFN- β to healthy volunteers. The IFN-induced metabolites are more sensitive to the presence of IFN than is a direct bioassay of IFN in serum. Up to 48 hours after oral IFN was administered, serum IFN or IFN-induced metabolites were not generally increased compared to pretreatment levels, *leading the authors to conclude that orally administered IFN had no significant biological effects*. (emphasis added). Witt PJ, et al, *J Interferon Res* 12:411-13 (1992).

Again, in a review of whether interferon can be effective when administered by oral route, Bocci observed that

[I]t appeared unreasonable to administer proteins and peptides per os because after swallowing either peptic or tryptic digestion would have ensued. . . Because IFNs are proteins . . . ,

they are promptly inactivated by hydrolytic enzymes and minimally absorbed via the mucosal surfaces . . . There is no doubt that adult animals, after swallowing IFN with saliva, inactivate most of it in the stomach . . . it is more realistic to assume that the majority of the (oral) IFN is lost in the mucous layer (after) the latter is swallowed, but certainly some binds to epithelial cell receptors.

Bocci V., *J Biol Reg Homeostasis Agents* 4:81-83 (1990).

Finally, in another publication, including one co-authored by Cummins, it was stated 'because IFNs are proteins and are inactivated by trypsin and other proteolytic enzymes and because IFN cannot be detected in the blood after oral administration, IFN administration by the oral route is not practiced in human medicine' (Cummins J, et al., *Journal of Biological Response Modifiers* 7(5):513-23 (1988).

As the art developed, a different dogma became common; the view Cummins takes in his patent, namely, that the key to administration of type one interferon is maximum contact of the substance with the oral and pharyngeal mucosa. In a publication co-authored by Cummins, the discussion section poses the question "is there is something special about the IFN in the oral epithelium?", only to answer that "the oral epithelium interacts in some unique manner with IFNs to induce systemic alterations in host defense mechanisms. A likely candidate would be IFN-induced biological response modifier(s) produced by the uniquely differentiated layers of the cells in the oral epithelium". (emphasis added) (A review

Article - Interferon administration by the oral route, 1993 Amarillo Cell Culture Co, Inc). Clearly again, Cummins maintains the view that it is contact with the oral and pharyngeal mucosa that is the key to type one interferon administration.

A study reported by Cummins in the same article, reports that Diez et al., (*J Interferon Res* 7:553-557 (1987)), made an interesting observation while studying the fate of I.V. radiolabelled recombinant HuIFN α in patients with numerical dynamic scintigraphy. The IFN-tracer could be found transiently but in significant amounts in the mouth, nose, and paranasal sinuses about 1 hour post-infusion, and that this significant accumulation in the area of the oral epithelium certainly suggested that IFN targets these tissues. Additionally, Cummins reported further evidence to support his interpretation: in another study where rats were injected I.V. with radiolabeled HuIFN- α and dynamic scintigraphy was performed, the majority of the labeled IFN concentrated in the head and neck region; i.e., most of the IFN-label was found to be localized in oral epithelium." (A review Article - Interferon administration by the oral route, 1993 Amarillo Cell Culture Co, Inc).

Moreover, another article, on which Cummins is a co-author, Leece, JG, et al., *J Mol Biotherapy* 2:211-216 (1990), describes the use of oral natural human interferon alpha in the treatment of rotavirus infection in neonate and weanling pigs, stating the IFN was given "in the oral cavity by syringe", and that administration "in the

oral cavity provides protection". Additionally, "oral administration of IFN α has generally been rejected because IFNs are susceptible to inactivation by proteolytic enzymes and not detected in the blood after oral administration".

Clearly Cummins taught, and those with average knowledge in the of the art agreed, if type one interferon *could* be administered by mouth, that it must be done so as to allow the drug to be retained in the patient's mouth (see Koech DK, et al., *Molecular Biotherapy* 2:91-95 (1990) (specifically formulated HuIFN α in powdered maltose and dispensed as a powder should be retained in the patient's mouth for 1-2 minutes to promote mucosal absorption before swallowing); Koech D, et al., *East African Medical Journal* 67(7 suppl 2):SS64-70 (1990) ([the dose should be] "placed in the mouth and allowed to dissolve in the saliva for 2-3 minutes, massaging gently with the tongue to facilitate ease of dissolution and effective mucosal contact...[t]he saliva is retained in the mouth for a further 2 minutes before swallowing."); (Caban J, et al., *Archivum Immunologiae et Therapiae Experimentalis* 41(3-4):229-35 (1993) (patients were instructed to allow the lozenge to dissolve in saliva, swirl the dissolved lozenge around the oral cavity to promote oral mucosa absorption prior to swallowing or keep the lozenge in the oral cavity until it completely dissolved with "food intake restricted 30 minutes before and after treatment)).

Applicant could cite multiple other articles reaching the same conclusion as those cited above: maximum contact with the oral and pharyngeal mucosa is the essential requisite for oral administration of type one interferons. Clearly each one of these publications expressly teaches away from the invention at hand. Not one publication teaches that effective treatment with type one interferons may be had by simple oral administration, i.e., immediate ingestion of the interferon. The point is that the present application was not anticipated or obvious in light of the prior art; and in fact, the results reached were completely unexpected in view of the ideology in the art at that time. Thus, Applicant contends, not only does Cummins not anticipate or render the present claims obvious, Cummins expressly teaches away from the current invention.

As the Examiner's primary reference does not anticipate or render obvious any of Applicant's independent claims, Applicant believes all dependent claims addressing, *inter alia*, dosage amounts and regimens, are not obvious. Thus, in view of the amendments and the remarks above, Applicants respectfully request that the rejections of claims 1-20 under 35 U.S.C. § 102(a) and 35 U.S.C. § 103 be withdrawn.

Applicant has enclosed a copy of each reference cited above for the Examiner's review. In addition, Applicant has enclosed herein copies of the references cited on pages 66-67 of the

specification as filed. Applicant regrets the delay in the submission of these publications and any inconvenience it may have caused.

Should the Examiner have any questions about the references or the application, or if the completion of prosecution of the present application can be facilitated in any way, the Examiner is requested to call the undersigned attorney.

This Response is intended to be a complete response to the Office Action mailed July 16, 1997. Applicant respectfully submits that claims 1-20 are in condition for allowance.

Respectfully submitted,



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